

Projected Risks and Health Benefits of Vaccination against Herpes Zoster and Related Complications: Interim Results

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Conflict of interest statement

Authors have no known conflicts of interest.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Objective

- To evaluate the tradeoffs between benefits of averted cases of herpes zoster and complications and risks of potential adverse events, specifically Guillain-Barré syndrome

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Methods: Risk-Benefit Analysis

- Existing simulation model used to estimate health outcomes, incorporating new data on Guillain-Barré syndrome (GBS)
 - Model structure: state-transition cohort model (n=1,000,000)
 - Outcome measures: projected cases of herpes zoster (HZ), postherpetic neuralgia (PHN), complications, deaths, and GBS [no quality-adjusted life years (QALYs)]
 - Cycle length: annual
 - Model inputs: published evidence, primary data, expert opinion

Prosser LA, et al. A cost-effectiveness analysis of vaccination for prevention of herpes zoster and related complications: input for national recommendations. *Ann Intern Med.* 2019;170(6):380-8.
- New data/revised assumptions
 - Health states added for GBS following HZ & GBS following vaccination with recombinant zoster vaccine (RZV); recurrent HZ excluded
 - 2-dose completion rate revised from 100% assumption in original analysis to 80-86%; 1-dose vaccine effectiveness (VE) updated
 - Unpublished data

Methods: Interventions

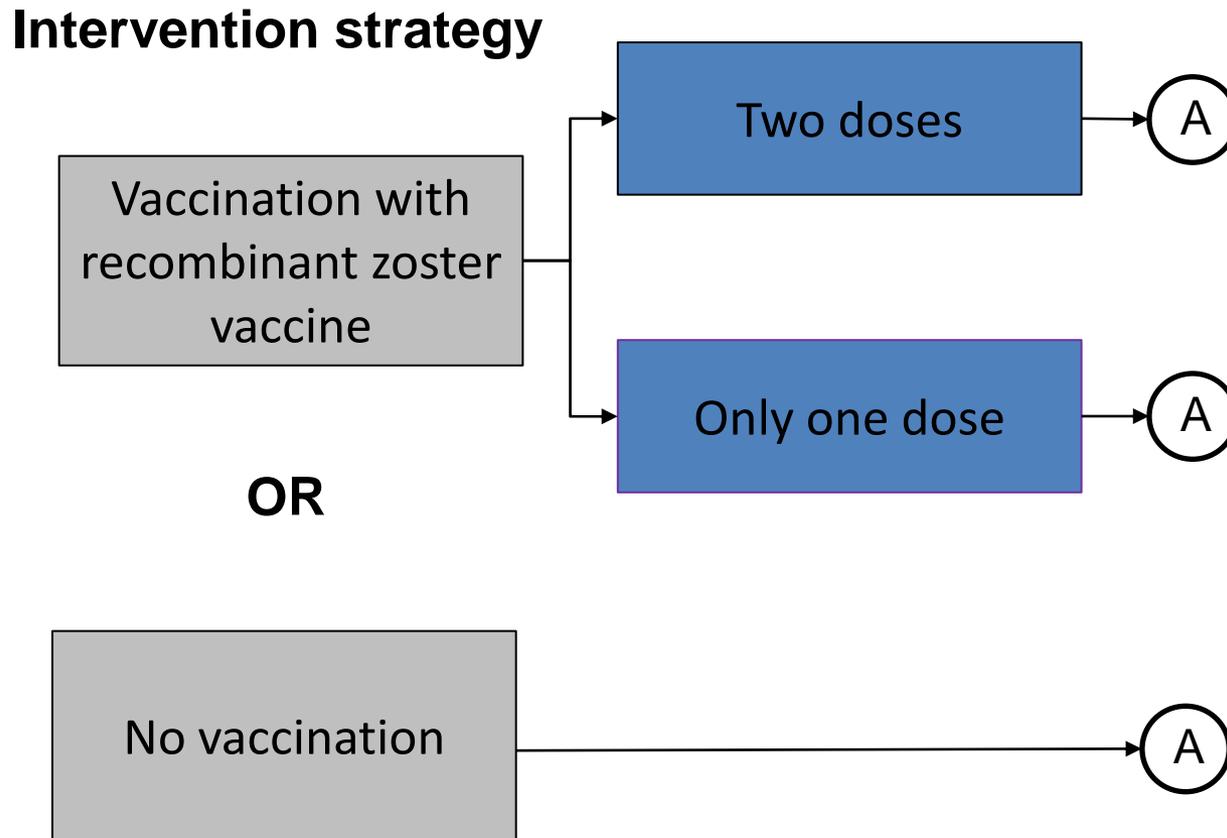
Strategies:

- 1. Vaccination with recombinant zoster vaccine (RZV)**
- 2. No vaccination**

Assumptions:

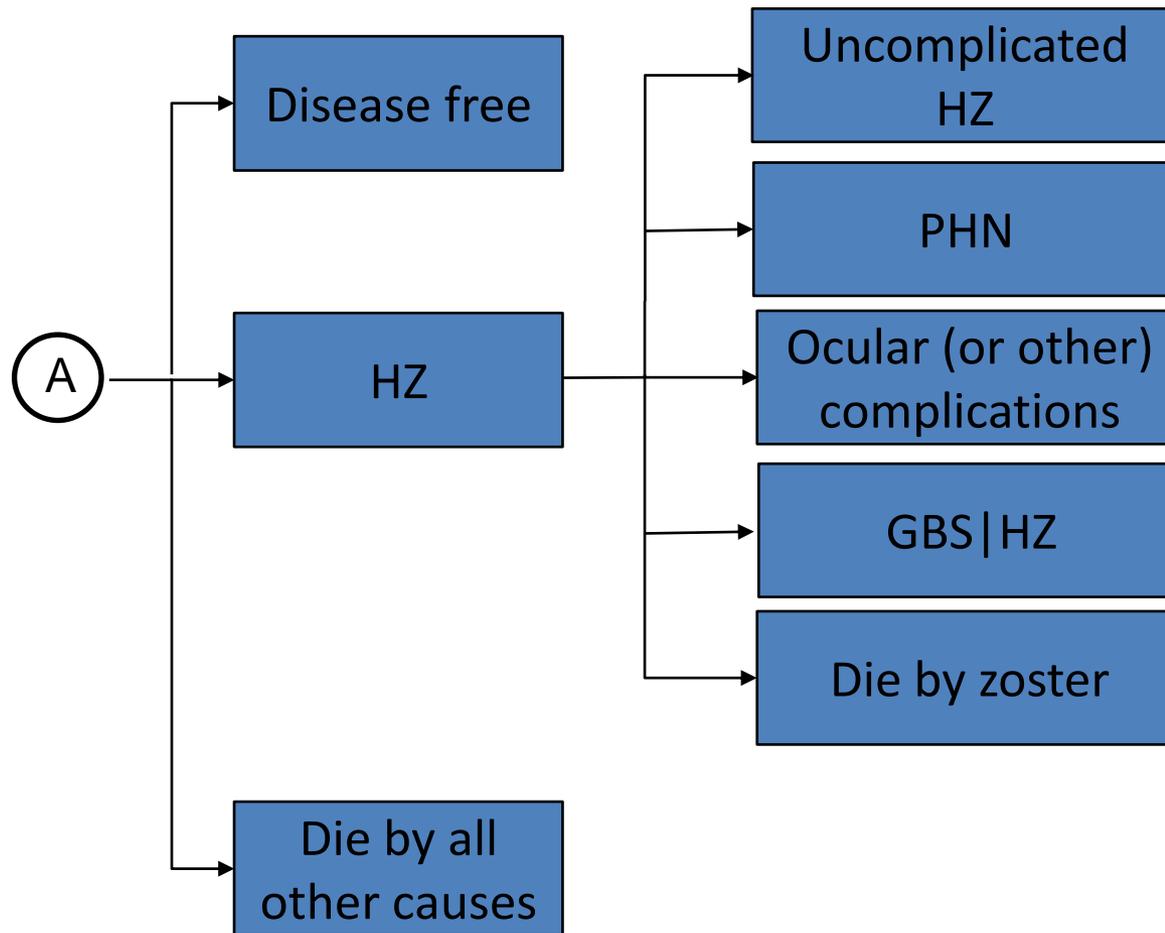
- 5 age-based cohorts: 50-59, 60-69, 70-79, 80-89, 90-99
- Analytic time horizon was vaccination age through 20 years (10y, lifetime)
- 2-dose series completion rate: 80% for 50-64y and 86% for 65+y (base case)
- Discount rate: 1.5% (0, 3%)

Methods: Simulation model (1)



Note: Please see the supplementary materials for a detailed model schematic

Methods: Simulation model (2)



Note: Please see the supplementary materials for a detailed model schematic

HZ= Herpes zoster; PHN= Postherpetic neuralgia; GBS=Guillain-Barré syndrome

2/25/21

Estimated probability of GBS associated with RZV

- VSD analysis, unpublished data (Nelson et al., presented ACIP, 10/2020)
 - Risk of GBS following RZV estimated using historical Zostavax (ZVL) comparator [3 cases in ZVL group: 1 unconfirmed]
 - Compared adverse event risks among 50-65 year-old RZV recipients (2018-2019) with 60-65 year-old ZVL vaccinees (2013-2017)
 - N = 647,307 doses
 - **Incremental risk difference** (pooled single-dose risk) per million doses
 - **2 confirmed cases:** 1.65 (-5.02, 8.33)
 - **3 confirmed cases:** 0.16 (-7.12, 7.45)
- FDA safety study, unpublished data
 - Risk of GBS following RZV estimated using self-controlled case series approach; Medicare data
 - Extended Study Period/PPV-Adjusted attributable risk (10/2017-2/2020)
 - N = 1,318,004 doses
 - **Attributable risk** (pooled single-dose risk) per million doses: 3.13 (0.62, 5.64)

Estimated probability of GBS associated with RZV

Parameter	Most Likely	Lower Bound	Upper Bound	Source
GBS RZV	Per 1,000,000*			
Pooled single dose risk (both doses)	1.65	0	8.33	VSD data <ul style="list-style-type: none"> • Conservative assumption • 2 confirmed cases in ZVL comparator, IRD: 1.65 (-5.02, 8.33) • Lower bound censored at zero; model cannot reflect “negative” cases; distribution for this parameter is modeled as a 2-part function
Dose 1 (single dose risk)**	3.30	0	13.6	
2-dose series, combined risk**	3.30	0	13.6	
Pooled single dose risk (both doses)	3.13	0.62	5.64	FDA safety study <ul style="list-style-type: none"> • AR for 2-dose series derived as 2x the pooled single-dose risk; dose 1 specific risk applied for individuals who do not complete 2-dose series • Study reports 0.22 rate ratio for 2nd-dose specific analysis – “protective effect” – consistent with lower estimated risk for 2-dose series
Dose 1 (single dose risk)	6.48	3.36	9.60	
2-dose series, combined risk**	6.26	1.24	11.3	

*Vaccinated (per million doses for single dose risks; per million vaccinated for the 2-dose series)

**Assumption

GBS=Guillain-Barré syndrome; RZV= Recombinant zoster vaccine; ZVL= Zoster vaccine live

New input parameters for GBS|HZ

- New health state added to model to estimate GBS following HZ
- Probability of GBS following HZ (unadjusted attributable risk estimates calculated using data from Anderson et al, *under review*)

Parameter	Most Likely	Lower Bound	Upper Bound	Source
GBS HZ	Per million HZ episodes			
18-64y	8.6	1.3	33.9	IBM MarketScan® data Anderson et al., <i>under review</i>
65+y	12.8	3.7	31.9	CMS Medicare data Anderson et al., <i>under review</i>

HZ= Herpes zoster; GBS=Guillain-Barré syndrome

Analysis Plan

- Base case analysis
- Uncertainty analyses
 - Probabilistic analysis
 - One-way sensitivity analyses, including time horizon, discount rate
 - Multi-way sensitivity analyses
- Best-case/worst-case analysis

Summary base case results, projected cases

20 year time horizon, discounted

Age group	Strategy	HZ (cases per million) †				
		Cases Uncomplicated	Cases PHN	Cases Ocular Complications	Deaths	Total HZ (cases +deaths)
50-59 years	Not vaccinated	87,173	12,562	9,871	110	109,681
	Vaccinated - RZV	49,578	7,038	5,505	62	62,284
60-69 years	Not vaccinated	98,034	19,211	11,609	129	128,984
	Vaccinated - RZV	51,387	9,861	6,604	67	67,380
70-79 years	Not vaccinated	88,131	22,350	10,959	329	121,771
	Vaccinated - RZV	42,756	10,412	5,274	158	58,600
80-89 years	Not vaccinated	61,355	19,148	7,986	240	88,730
	Vaccinated - RZV	21,581	6,728	2,808	84	31,202
90-99 years	Not vaccinated	35,907	13,650	4,916	147	54,621
	Vaccinated - RZV	7,735	2,897	1,055	32	11,719

† Cases per cohort. Each cohort includes 1 million individuals some proportion of whom experience HZ and some who do not. For example, for unvaccinated individuals 60-69 y, this includes 128,984 total cases HZ and 871,016 individuals without HZ, over the 20 year time horizon.

HZ= Herpes zoster; PHN= Postherpetic neuralgia; RZV= Recombinant zoster vaccine

Summary base case results, w/ cases of GBS

20 year time horizon, discounted

Age group	Strategy	Cases GBS RZV* (VSD)	Cases GBS RZV* (FDA)	HZ (cases per million) †					
				Cases Uncomplicated	Cases PHN	Cases Ocular Complications	Deaths	Cases GBS	Total HZ (cases +deaths)
50-59 years	Not vaccinated	-	-	87,173	12,562	9,871	110	0.9	109,681
	Vaccinated - RZV	3.3	6.3	49,578	7,038	5,505	62	0.5	62,284
60-69 years	Not vaccinated	-	-	98,034	19,211	11,609	129	1.4	128,984
	Vaccinated - RZV	3.3	6.3	51,387	9,861	6,604	67	0.7	67,380
70-79 years	Not vaccinated	-	-	88,131	22,350	10,959	329	1.6	121,771
	Vaccinated - RZV	3.3	6.3	42,756	10,412	5,274	158	0.8	58,600
80-89 years	Not vaccinated	-	-	61,355	19,148	7,986	240	1.1	88,730
	Vaccinated - RZV	3.3	6.3	21,581	6,728	2,808	84	0.4	31,202
90-99 years	Not vaccinated	-	-	35,907	13,650	4,916	147	0.7	54,621
	Vaccinated - RZV	3.3	6.3	7,735	2,897	1,055	32	0.2	11,719

*Cases per million RZV vaccinated (1 dose or 2-dose series)

† Cases per cohort. Each cohort includes 1 million individuals some proportion of whom experience HZ and some who do not. For example, for unvaccinated individuals 60-69 y, this includes 128,984 total cases HZ and 871,016 individuals without HZ, over the 20 year time horizon.

HZ= Herpes zoster; PHN= Postherpetic neuralgia; GBS=Guillain-Barré syndrome; RZV= Recombinant zoster vaccine

Summary base case results, cases & cases averted

20 year time horizon, discounted, 60-69y

Age group	Strategy	Cases GBS RZV* (VSD)	Cases GBS RZV* (FDA)	Cases HZ (per million) †					
				Cases Uncomplicated	Cases PHN	Cases Ocular Complications	Deaths	Cases GBS	Total HZ
60-69 years	Not vaccinated	-	-	98,034	19,211	11,609	129	1.4	128,984
	Vaccinated - RZV	3.3	6.3	51,387	9,861	6,604	67	0.7	67,380
	Incremental	3.3	6.3	(46,648)	(9,350)	(5,544)	(62)	(0.7)	(61,604)

*Cases per million RZV vaccinated (1 dose or 2-dose series)

† Cases per cohort. Each cohort includes 1 million individuals some proportion of whom experience HZ and some who do not. For example, for unvaccinated individuals 60-69 y, this includes 128,984 total cases HZ and 871,016 individuals without HZ, over the 20 year time horizon.

HZ= Herpes zoster; PHN= Postherpetic neuralgia; GBS=Guillain-Barré syndrome; RZV= Recombinant zoster vaccine

Summary base case results, cases & cases averted

20 year time horizon, discounted, all age groups

Age group	Strategy	Cases GBS RZV* (VSD)	Cases GBS RZV* (FDA)	Cases HZ (per million) †					
				Cases Uncomplicated	Cases PHN	Cases Ocular Complications	Deaths	Cases GBS	Total HZ
50-59 years	Not vaccinated	-	-	87,173	12,562	9,871	110	0.9	109,681
	Vaccinated - RZV	3.3	6.3	49,578	7,038	5,505	62	0.5	62,284
	Incremental	3.3	6.3	(37,559)	(5,524)	(4,266)	(47)	(0.4)	(47,397)
60-69 years	Not vaccinated	-	-	98,034	19,211	11,609	129	1.4	128,984
	Vaccinated - RZV	3.3	6.3	51,387	9,861	6,604	67	0.7	67,380
	Incremental	3.3	6.3	(46,648)	(9,350)	(5,544)	(62)	(0.7)	(61,604)
70-79 years	Not vaccinated	-	-	88,131	22,350	10,959	329	1.6	121,771
	Vaccinated - RZV	3.3	6.3	42,756	10,412	5,274	158	0.8	58,600
	Incremental	3.3	6.3	(45,375)	(11,938)	(5,685)	(171)	(0.8)	(63,170)
80-89 years	Not vaccinated	-	-	61,355	19,148	7,986	240	1.1	88,730
	Vaccinated - RZV	3.3	6.3	21,581	6,728	2,808	84	0.4	31,202
	Incremental	3.3	6.3	(39,774)	(12,421)	(5,178)	(155)	(0.7)	(57,528)
90-99 years	Not vaccinated	-	-	35,907	13,650	4,916	147	0.7	54,621
	Vaccinated - RZV	3.3	6.3	7,735	2,897	1,055	32	0.2	11,719
	Incremental	3.3	6.3	(28,171)	(10,753)	(3,861)	(116)	(0.5)	(42,902)

*Cases per million RZV vaccinated (1 dose or 2-dose series)

† Cases per cohort. Each cohort includes 1 million individuals some proportion of whom experience HZ and some who do not. For example, for unvaccinated individuals 60-69 y, this includes 128,984 total cases HZ and 871,016 individuals without HZ, over the 20 year time horizon.

HZ= Herpes zoster; PHN= Postherpetic neuralgia; GBS=Guillain-Barré syndrome; RZV= Recombinant zoster vaccine

Projected incremental cases GBS & averted cases HZ

20 year time horizon, discounted

Age group	Strategy	Cases GBS RZV* (VSD)	Cases GBS RZV* (FDA)	Averted Cases HZ (per million) †					
				Uncomplicated	PHN	Ocular Complications	Deaths	GBS	Total HZ
50-59 years	Vaccinated	3.3	6.3	(37,559)	(5,524)	(4,266)	(47)	(0.4)	(47,397)
60-69 years	Vaccinated	3.3	6.3	(46,648)	(9,350)	(5,544)	(62)	(0.7)	(61,604)
70-79 years	Vaccinated	3.3	6.3	(45,375)	(11,938)	(5,685)	(171)	(0.8)	(63,170)
80-89 years	Vaccinated	3.3	6.3	(39,774)	(12,421)	(5,178)	(155)	(0.7)	(57,528)
90-99 years	Vaccinated	3.3	6.3	(28,171)	(10,753)	(3,861)	(116)	(0.5)	(42,902)

*Incremental cases per million RZV vaccinated (1 dose or 2-dose series)

† Cases per cohort. Each cohort includes 1 million individuals some proportion of whom experience HZ and some who do not. For example, for unvaccinated individuals 60-69 y, this includes 128,984 total cases HZ and 871,016 individuals without HZ, over the 20 year time horizon.

HZ= Herpes zoster; PHN= Postherpetic neuralgia; GBS=Guillain-Barré syndrome; RZV= Recombinant zoster vaccine

Probabilistic sensitivity analysis

20 year time horizon, discounted, 60-69 years

Base case values (95% CI)

Age group	Strategy	Cases GBS RZV (per million)	Cases GBS HZ (per million)	Total, GBS HZ and GBS RZV (per million)	Incremental total GBS cases, (per million)†
60-69y (VSD)	Not vaccinated	-	1.4 (0.3; 3.3)	1.4 (0.3; 3.3)	-
	Vaccinated-RZV	3.3 (0.0; 12.7)	0.7 (0.1; 1.6)	4.0 (0.2; 13.3)	2.6 (-1.6, 11.8)
60-69 y (FDA)	Not vaccinated	-	1.4 (0.3;3.3)	1.4 (0.3; 3.3)	-
	Vaccinated-RZV	6.3 (2.0; 10.6)	0.7 (0.1; 1.6)	7.0 (2.5; 11.3)	5.6 (1.2, 9.9)

Projected incremental cases GBS & averted cases HZ

20 year time horizon, discounted

Age group	Strategy	Incr. Cases GBS (VSD)*	Incr. Cases GBS (FDA)*	Averted Cases HZ (per million)†				
				Uncomplicated	PHN	Ocular Complications	Deaths	Total HZ
50-59 y	Vaccinated	2.9	5.9	(37,559)	(5,524)	(4,266)	(47)	(47,397)
60-69 y	Vaccinated	2.6	5.6	(46,648)	(9,350)	(5,544)	(62)	(61,604)
70-79 y	Vaccinated	2.5	5.5	(45,375)	(11,938)	(5,685)	(171)	(63,170)
80-89 y	Vaccinated	2.6	5.6	(39,774)	(12,421)	(5,178)	(155)	(57,528)
90-99 y	Vaccinated	2.8	5.7	(28,171)	(10,753)	(3,861)	(116)	(42,902)

*Cases per million RZV vaccinated (1 dose or 2-dose series)

† Cases per cohort. Each cohort includes 1 million individuals some proportion of whom experience HZ and some who do not. For example, for unvaccinated individuals 60-69 y, this includes 128,984 total cases HZ and 871,016 individuals without HZ, over the 20 year time horizon.

HZ= Herpes zoster; PHN= Postherpetic neuralgia; GBS=Guillain-Barré syndrome; RZV= Recombinant zoster vaccine

Limitations

- Reliance on unpublished data for key parameters
- Limited data available
- Challenges of characterizing rare events
- Quality-adjusted life years not included

Summary

- Evaluated tradeoffs between benefits of averted cases of HZ and complications and risks of rare adverse events
- Estimated outcomes per 1,000,000 vaccinated individuals
 - Averted cases of HZ, PHN, other complications (e.g., GBS), and deaths
 - Rare adverse events (e.g., GBS)
- Projected cases of GBS are sensitive to parameter uncertainty
- Estimates of averted cases of HZ, complications, and deaths rely on published data and less sensitive to changes in parameter inputs